Deactivation to antineoplastic agents

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Deactivation to antineoplastic agents is becoming a standard of care in hemato-oncology. Hypersensitivity to antineoplastic drugs represents an increasing problem in oncology due to the use of an expanded repertoire of different agents. Additionally, since these (new) agents show a higher efficacy, patients are exposed to the same antineoplastic drug for a longer time period resulting in a higher chance of sensitization. Once sensitization to a certain antineoplastic drug is present, therapy has to be modified, irrespective of its efficacy. Treatment modifications avoiding drugs causing hypersensitivity may affect the course of the disease and life expectancy. Therefore, therapeutic interventions are needed to allow the continuation of efficient antineoplastic drugs even if a hypersensitivity reaction has occurred.

As an example, hypersensitivity reactions to carboplatin and oxaliplatin occur frequently. Both these drugs are commonly used as part of poly-chemotherapy–regimens. Incidences of 12% to 17% of hypersensitivity reactions have been reported for these treatment modalities in the literature. More than 50% of the reported reactions were classified as moderate to severe [1-3].

To illustrate the typical clinical situation we should like to present the following case. A 42 year old male patient was diagnosed with borderline resectable adenocarcinoma of the pancreatic head. Surgical exploration was performed at another hospital, but resection was not attempted due to unexpectedly extensive invasion of the superior mesenteric vein. The patient was started on induction chemotherapy with FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin) in an effort to downsize the tumor. During the first cycle of FOLFIRINOX the patient developed swelling of the tongue, slight dyspnea and a skin rash 20 min after the start of the irinotecan application. The infusion had to be stopped and the symptoms slowly resolved after administration of steroids and antihistamines. Irinotecan was re-administered 2 weeks later causing a similar and more pronounced reaction. The treating oncologist was convinced that irinotecan had to be discontinued. After contacting our institution he agreed to transfer the patient for an attempt to deactivation. We successfully treated the patient with a third cycle of FOLFIRINOX infusing irinotecan in a hyperfractionated manner without any signs of hypersensitivity reaction. After 2 additional cycles of FOLFIRINOX (with hyperfractionated irinotecan) a complete resection of the pancreatic adenocarcinoma with reconstruction of the superior mesenteric vein could be performed. Postoperatively, FOLFIRINOX with hyperfractionated irinotecan was successfully given for another eight cycles again without any signs of hypersensitivity.

Hypersensitivity to drugs presents with a wide variety of clinical symptoms and can be graded from mild to serve (Table 1). Clinical presentation depends on the underlying immunological mechanism. In the 1960s Coombs and Gell presented the concept of four mechanisms by which substances including drugs can cause hypersensitivity reactions. Additional knowledge about the activation of T cells has led to the modification of the description of the T-cell mediated drug hypersensitivity (Table 2 [4]). Type I reactions have a rather typical presentation with symptoms of an immediate type reaction arising within one hour (rarely several hours) after drug application. The manifestation of our clinical case would be considered a moderate to severe immediate type reaction. By contrast, T-cell mediated late type reactions take place one hour to several days after drug administration.

The first challenge in onco-allergology is to identify the drug that is most likely responsible for the hypersensitivity reaction. In the majority of cases chemotherapy regi-

Table 1: Clinical grading of immediate type reactions

GRADE	MILD	MODERATE	SEVERE
CLINICAL FEATURES	cutaneous and subcutaneous only	cardiovascular, respiratory, or gastrointestinal involvement	hypoxia, hypotension or neurologic compromise
DEFINING SYMPTOMS AND SIGNS	Generalized erythema, periorbital edema, urticarial or angioedema	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness, diaphoresis, chest or throat tightness, abdominal pain	cyanosis or SpO2 ≤92% at any stage, hypotension (systolic BP < 90 mmHg in adults), confusion, collapse, loss of consciousness, or incontinence

	Type of immuneresponse	Pathophysiology	Clinical symptoms	Typical chronology of the reaction
I	IgE	Mast cell and basophil degranulation	Anaphylactic shock Angioedema Urticaria Bronchospasm	Within 1 to 6 h after the last intake of the drug
II	IgG and complement	IgG and complement-dependent cytotoxicity	Cytopenia	5–15 days after the start of the eliciting drug
III	IgG or IgM and complement or FcR	Deposition of immune complexes	Serum sickness Urticaria Vasculitis	7–8 days for serum sickness/ urticaria 7–21 days after the start of the eliciting drug for vasculitis
IV a	Th1 (IFNγ)	Monocytic inflammation	Eczema	1–21 days after the start of the eliciting drug
IV b	Th2 (IL-4 and IL-5)	Eosinophilic inflammation	Maculopapular exanthema, DRESS	1 to several days after the start of the eliciting drug for MPE 2–6 weeks after the start of the eliciting drug for DRESS
IV c	Cytotoxic T cells (granzyme B, perforin, FasL)	Keratinocyte death mediated by CD4 or CD8	Maculopapular exanthema, SJS/TEN, pustular exanthema	1–2 days after the start of the eliciting drug for fixed drug eruption 4–28 days after the start of the eliciting drug for SJS/TEN
IV d	T cells (IL-8/ CXCL8)	Neutrophilic inflammation	Acute generalized exanthematous pustulosis	Typically 1–2 days after the start of the eliciting drug (but could be longer)

Table 2: Classification of drug allergies (published in [4]), maculopapular exanthema (MPE), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

mens consist of multiple drugs given over a few hours, often combined with antiemetic drugs.

Therefore, a hypersensitivity reaction to a drug can occur during the infusion of another drug applied subsequently, rendering the identification of the culprit elicitor very difficult. The problem is even more difficult in the situation of a late type reaction occurring after all drugs of a treatment regimen have been applied. To potentially identify the responsible drug of an IgE-mediated reaction, the method of choice is prick and/or intracutaneous testing. The knowledge on skin testing with anti-neoplastic drugs is improving; however, certain substances cannot be tested in the skin because of their necrotizing effect or due to the fact that non-irritant skin test concentrations have not yet been identified and published for many drugs (i.e. anthracyclines). In general, the sensitivity of skin testing is rather low [4]. At the same time, patients may be in urgent need to receive their anti-neoplastic treatment. Given the difficulty to perform clinical trials in patients with allergic reactions to anti-neoplastic drugs, pragmatic decisions have to be made with the aim to allow continuation of an effective poly-chemotherapeutic regimen. In addition to the practical need and beside the theoretical knowledge about drug hypersensitivity the underlying pathophysiologic mechanism of an individual hypersensitivity reaction will remain undefined in most cases. The algorithm described below is considered a deactivation protocol and not a desensitization protocol since no long term tolerance to the cytotoxic agents will be initiated. Therefore, every administration of the suspected drug has to be done as part of deactivation protocol.

When hypersensitivity to an antineoplastic drug is suspected, we use the following algorithm at our institution: First, the patient has to be precisely interviewed about the clinical reaction and the patient's chart has to be critically reviewed in order to identify the drug with the highest likelihood of being responsible (medical history). Second, the oncologist has to evaluate alternative anticancer treatments without the suspected antineoplastic drug. If no valid alternative is available and the reaction is clinically assumed to represent an immediate-type hypersensitivity reaction, a desensitization protocol can be considered (medical need). If no prompt administration of the next cycle of chemotherapy is needed and the knowledge for non-irritant and established skin test concentration is

available, prick and intracutaneous testing is performed at the Department of Dermatology (Allergy Unit) (testing). Ideally, skin testing is performed with various concentrations of the suspected drug to increase the knowledge of non-irritant concentrations of cytotoxic agents. Furthermore, plasma tryptase level is measured in all patients with immediate type reaction to rule out the possibility of an underlying mastocytosis. Specifically, since tryptase is a marker of mast cell degranulation during an allergic IgE-mediated reaction, it should be measured at 1 to 4 hours after an adverse infusion reaction has occurred. Measurement of increased serum tryptase concentration supports the suspicion that a reaction may be IgE mediated.

Finally, deactivation treatment is performed applying the following considerations. For reactions considered to be of the immediate type we use a 12-step hyperfractionated deactivation protocol [5]. Deactivation treatment is usually not performed for cytotoxic drugs causing late type reactions. Importantly, deactivation treatment is contraindicated , if the patient had developed severe skin reactions such as Stevens-Johnson-Syndrom, Lyell-Syndrom or DRESS (Drug Rash with Eosinophilia and Systemic Symptoms).
Patients are treated with anti-histamines and steroids 12 hours and one hour before the start of the deactivation protocol. The protocol is designed to increase the administered concentration of the anti-neoplastic drug every 15 min until the final dose is reached within approximately 6 hours. For the first deactivation treatment the patient is admitted to the intensive care unit to insure close monitoring of vital signs and immediate medical intervention in case of an adverse reaction. For the first hyperfractionated application only a single suspected drug is applied. The remaining substances of the poly-chemotherapy regimen are administered one day later with the exception of antiemetic drugs. When tolerance is good, further applications are performed in an outpatient setting and the remaining drugs of poly-chemotherapy can be given after the hyperfractionated drug application on the same day.
In all cases the deactivation protocol has to be closely monitored by a physician to insure prompt intervention in case of any hypersensitivity reaction. The treatment of choice for a severe hypersensitivity reaction is adrenalin injected intramuscularly followed by intravenously injected antihistamines [6]. Steroids have no effect in the first minutes of the allergic reaction but show a late phase effect.

So far, we have used such hyperfractionated deactivation protocols for treating patients with mild to severe allergic reactions to the following drugs: rituximab, tocilizumab, irinotecan, carboplatin and taxanes. We were able to give the drugs at therapeutic doses in all patients. Thus, before changing the anti-neoplastic drugs to a potentially less effective alternative because of hypersensitivity reactions, a hyperfractionated application should be considered, preferably applied at a center with experience in deactivation treatments.

References:

1. **Markman M, Kennedy A, Webster K, Elson P, Peterson G and others.** 1999. Clinical features of hypersensitivity reactions to carboplatin. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **17**:1141.
2. **Limsuwan T, Castells MC.** 2010. Outcomes and safety of rapid desensitization for chemotherapy hypersensitivity. *Expert opinion on drug safety* **9**:39-53.
3. **Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A and others.** 2003. Hypersensitivity reactions related to oxaliplatin (OHP). *British journal of cancer* **89**:477-81.
4. **Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM and others.** 2014. International Consensus on drug allergy. *Allergy* **69**:420-37.
5. **Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA and others.** 2008. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *The Journal of allergy and clinical immunology* **122**:574-80.
6. **Dhami S, Panesar SS, Roberts G, Muraro A, Worm M and others.** 2014. Management of anaphylaxis: a systematic review. *Allergy* **69**:168-75.

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